Pre-existing Conditions and Risk of Mortality

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Abstract

Background

Chronic diseases such as hypertension, diabetes, stroke, and coronary heart disease are concerning disease states that contribute to decreased quality of life, increased hospitalizations and mortality[1,2]. Metabolic syndrome, though not categorized as a chronic disease, involves a set of conditions that may predispose individuals to disease states[3,4]. This study aimed to study the relationships between pre-disease and disease states and mortality.

Methods

We studied 4273 subjects from Framingham Heart Study dataset. A new proxy variable for metabolic syndrome was created to account for pre-existing metabolic anomalies among participants. Kaplan-Meier univariate survival analysis, Cox Proportional Hazards Models, and Poisson logistic regression models were used to analyze the association between pre-existing conditions (hypertension, diabetes, stroke and coronary heart disease) and pre-disease condition (metabolic syndrome) with risk of mortality.

Results

After adjusting for age and gender, pre-existing conditions and number of pre-existing conditions remained significant predictors of mortality. Metabolic syndrome alone was a significant predictor of mortality, however, it loses significance after adjusting for pre-existing hypertension. Smoking intensity was associated with higher mortality rate even after adjusting for pre-existing conditions, age, and gender.

Conclusion

Pre-existing conditions and smoking intensity were significantly associated with higher mortality. Preventing hypertension, diabetes, stroke, coronary heart disease, and reducing smoking may prolong life expectancy. Prevention may be targeted towards individuals with metabolic syndrome as this pre-disease state may be associated with increased mortality. The best route of prevention may be through blood pressure control.

Methods

The dataset that we used is a portion of dataset that originated from the Framingham Heart Study, a cardiovascular cohort study of residents in Framingham, Massachusetts since 1948. We created a new variable, metabolic syndrome, which is a proxy binary variable based on the official clinical definition of metabolic syndrome[3,4], with the conditions of total cholesterol greater than 240, systolic blood pressure greater than 130 or use of antihypertensive medication at the time of the exam, and a body mass index category 2 or above (BMI > 25). Pre-existing conditions were defined as disease states that were present in an individual at time of enrollment and included diabetes, hypertension, coronary heart disease, and stroke. Number of pre-existing conditions were defined as 0 for no conditions, 1 for 1 condition, and 2 for greater than 2 conditions. We dropped observations with missing data for the variables we used in our models: serum total cholesterol in mg/dL, systolic blood pressure, the use of antihypertensive medication, body mass index categories, diabetes, pre-existing hypertension, pre-existing coronary heart disease, pre-existing episodes of stroke, age categories, gender, the number of cigarettes that one smokes per day, and whether or not one currently smokes cigarettes. From the original number of 4434 subjects, we ended up with 4273 subjects for our study. The goal of this study was to explore the association between pre-existing conditions, pre-disease state

(metabolic syndrome), and risk of mortality. We further assessed the relationship between these conditions and smoking in predicting mortality.

To answer our study questions, we initially performed an univariate Kaplan-Meier survival analysis (significance determined via log rank test) for all covariates of interest. We then analyzed models with and without smoking using both Cox proportional hazards and Poisson. For each finalized model, we added age categories, gender, cigarettes per day to control for confounding by these covariates, as adding these covariates changed the coefficients of others

(metabolic syndrome, hypertension, diabetes, coronary heart disease, stroke, and number of pre-existing conditions) in the models by over 10% for the cox proportional hazards model. For the poisson model, the coefficient for metabolic syndrome changed by over 10%, but the coefficients for the other covariates (hypertension, diabetes, coronary heart disease, stroke, and number of pre-existing conditions) did not, suggesting that these covariates may not be strong confounders for the Poisson model. We included the interaction between sex and cigarettes per day as there was significant effect modification between these two covariates. We noted that two of the covariates (pre-existing conditions and age categories) did not satisfy the proportional hazards assumption (assessed via Cox PH assumptions test and Schoenfeld residuals). To correct for the deviation from proportional hazards, we stratified on those two covariates in separate, stratified models (Table 2). We noted that when we stratified these two covariates, the effect modification of smoking on gender was no longer significant, however, we included the effect modification in our stratified model for ease of comparison. We considered Poisson extensions by assessing the deviance of our Poisson model and found that the test result was not statistically significant. Therefore, it was not necessary to adjust for overdispersion with a negative binomial model or robust variance model. We considered but did not see a need for zero-inflated Poisson model, as our outcomes were based on mortality overtime, which should not have structural zeros. Analysis was performed using R 3.3.3.

Results

From a population of 4273 patients, we found that the most prevalent pre-existing condition was hypertension (32%), while the least prevalent was stroke (0.6%). Our proxy metabolic syndrome encompassed 710 patients (17% of patients). From summary statistics of our patient population in Table 1a, we noted that patients with pre-existing coronary heart disease had the highest mean age, while pre-existing hypertension had the lowest (57.7 vs 53.8). Metabolic syndrome had the highest proportion of females, whereas coronary heart disease had the lowest (60% vs 36%). We noted that a majority of patients in our study population had 0 pre-existing conditions, and patients with higher number of pre-existing conditions have a higher mean age (Table 1b). Interestingly, there was a lower percentage of smoking and degree of smoking intensity in patients with higher number of pre-existing conditions, though smoking and a higher number of pre-existing conditions were associated with higher mortality (Table 2). After a preliminary Kaplan-Meier univariate survival analysis, we found that metabolic syndrome conferred significant mortality risks (Figure 1a), though the risk was less in magnitude than pre-existing conditions, such as diabetes (Figure 1b). A current smoking status led to an increase in mortality regardless of the number of pre-existing conditions that were manifested at the beginning of study (Figure 2).

By exploring both Cox Proportional Hazards and Poisson models, we found that age and gender were significant confounders and predictors of the effects of pre-existing conditions and number of pre-existing conditions on mortality. Furthermore, smoking was both a general confounder (for Cox model only) and an effect modifier for gender on mortality (for both models), though the significance of smoking disappears with stratification in our Cox model. Our final models included pre-existing conditions or number of pre-existing conditions, metabolic syndrome, age categories, gender, and smoking intensity (Table 2). Overall, we found that the unstratified Cox models consistently perform better than stratified based on AIC, however due to proportional hazard violations, we opted for the stratified model for our final results. Furthermore, our model for separate pre-existing conditions appears to be a better fit than our model for number of pre-existing conditions (based on AIC), suggesting that though the number of pre-existing conditions is an important point of consideration in the prediction of hazard ratios of mortality, the specific pre-existing conditions involved are better predictors of mortality. Finally, we observe that hazards ratios for mortality were significantly increased in individuals with pre-existing diabetes (2.60-3.08 across age categories, p value < 0.01), coronary heart disease (2.27-3.11 across age categories, p value < 0.01), or previous episodes of stroke (2.40-2.64 across age categories, p value < 0.01) at the initiation of study compared to those who did not. The hazard ratios for mortality were significantly increased in those with pre-existing hypertension as well, though the increase was less pronounced (2.10-2.34 across age categories, p value < 0.01). Hazard ratios for mortality varied widely between strata of age categories and number of pre-existing conditions, with protective effects in individuals without pre-existing conditions (0.37-0.43 across age categories, p value < 0.01), and the greatest increased risk of mortality in individuals with two or more pre-existing conditions (3.67-5.12 across age categories, $p < 0.01$). Per unit increase in cigarettes per day was associated with a 2.01 increase in hazard ratio of mortality among males and a 3.02 increase in hazard ratio of mortality among females in our unstratified Cox model. Though metabolic syndrome was not statistically significant as a predictor in our full model, we included it in our model as it was a variable of great interest in our study. We found that in general, incidence ratios for mortality (estimated using Poisson model) were less pronounced in magnitude than hazard ratios (Cox model). Whereas both estimate the rate of mortality across a period of time within a study population, Poisson assumes that baseline hazard rate remains the same while Cox allows more flexibility in our modeling by allowing baseline hazard rate to change. In this manner, we believe that the Cox model is a superior model for our purposes as the baseline hazard rate for mortality general increases as people age overtime.

Some limitations of our study include the use of a proxy set of conditions for metabolic syndrome in our dataset as opposed to complete adherence to the official criteria, as our dataset did not have sufficient information on fasting glucose levels or waistline measurements. In this manner, our metabolic syndrome covariate may be overly influenced by high blood pressure factors. This may be further evidenced by our observation that metabolic syndrome no longer remains significant after adjusting for pre-existing hypertension, suggesting that it may have largely collinear effects with hypertension on mortality. As we stratify our dataset in an attempt to correct for deviation from Cox proportional hazards assumption, another concern may be over-stratification, leading to overfitting of our dataset which reduces our models external relevance and decreasing power (which may have led to our observations that smoking was no longer significant after stratification and AIC values suggesting worse fit after stratification). Another way to correct for these deviations may be the inclusion of time-dependent variables, which we did not perform here. Another major limitation of our study is that we assessed only the effects of conditions that existed before study initiation on mortality, though conditions that developed in the timespan of the study should also have significant effect on survival.

References

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Table 1: Baseline Characteristics among Participants with Pre-existing Conditions or Metabolic Syndrome

a. Pre-existing conditions

	Metabolic syndrome* No. (%)	Hypertension No. (%)	Diabetes No. (%)	Coronary heart disease No. (%)	Stroke No. (%)
n (sample size)	710	1372	115	182	28
Gender					
M	285 (40%)	616 (45%)	56 (49%)	116 (64%)	13 (46%)
F	425 (60%)	756 (55%)	59 (51%)	66 (36%)	15 (54%)
Age (mean, sd)	53.9 (7.63)	53.8 (8.16)	55.6 (7.35)	57.7 (7.47)	55.7 (7.39)
Smoking status					
Current smoker					
Yes	268 (38%)	564 (41%)	39 (34%)	79 (43%)	10 (36%)
No	442 (62%)	808 (59%)	76 (66%)	103 (56%)	18 (64%)
Cigarettes per day (mean, sd)	7.38 (12.2)	7.69 (11.9)	5.92 (9.59)	8.14 (12.3)	5.11 (7.59)

b. Number of pre-existing conditions

	0 No. (%)	1 No. (%)	2+ No. (%)
n (sample size)	2770	1324	179
Gender			
M	1186 (43%)	624 (47%)	85 (47%)
F	1584 (57%)	700 (53%)	94 (53%)
Age (mean, sd)	47.7 (8.13)	53.3 (8.17)	58.2 (6.64)
Smoking status			
Current smoker			
Yes	1459 (53%)	564 (43%)	62 (35%)
No	1311 (47%)	760 (57%)	117 (65%)
Cigarettes per day (mean, sd)	9.53 (11.8)	8.30 (12.4)	5.05 (8.90)

Table 2 Pre-existing Conditions, Metabolic Syndrome, Cigarettes Density and Mortality Risk

a. Model 1 (Pre-existing Conditions)

	Proportional Hazards (Hazard Rate Ratio)					Poisson (Incidence Rate Ratio)
Model 1	mortality ~ metabolic + prevhyp + diabetes + prevchd + prevstrk + age + sex + cigarettes per day + sex * cigarettes per day					
	Without stratification	With stratification				
		agecat 1	agecat 2	agecat 3	agecat4	
AIC	22979.55	23408.90	23373.52	23523.92	23185.54	6785.08
Metabolic syndrome HR/OR (95% CI); p	1.03 (0.80, 1.32); 0.81	1.12 (0.87, 1.43); 0.38	1.21 (0.94, 1.55); 0.14	1.20 (0.93, 1.53); 0.16	1.18 (0.92, 1.51); 0.20	1.03 (0.80, 1.31); 0.79
Prevalent hypertension HR/OR (95% CI); p	1.83 (1.65, 2.04); <0.01	2.20 (1.97, 2.44); <0.01	2.25 (2.02, 2.50); <0.01	2.34 (2.10, 2.60); <0.01	2.10 (1.89, 2.34); <0.01	1.71 (1.54, 1.91); <0.01
Diabetes HR/OR (95% CI); p	2.46 (1.98, 3.05); <0.01	2.93 (2.36, 3.64); <0.01	2.94 (2.36, 3.65); <0.01	3.08 (2.48, 3.82); <0.01	2.60 (2.09, 3.23); <0.01	2.10 (1.68, 2.59); <0.01
Prevalent coronary heart disorder HR/OR (95% CI); p	2.10 (1.75, 2.52); <0.01	2.95 (2.46, 3.53); <0.01	2.77 (2.31, 3.32); <0.01	3.11 (2.60, 3.72); <0.01	2.27 (1.89, 2.72); <0.01	1.80 (1.49, 2.15); <0.01
Prevalent stroke HR/OR (95% CI); p	2.28 (1.48, 3.52); <0.01	2.64 (1.71, 4.08); <0.01	2.40 (1.56, 3.70); <0.01	2.60 (1.69, 4.01); <0.01	2.50 (1.62, 3.86); <0.01	1.97 (1.24, 2.95); <0.01
Age HR/OR (95% CI); p	2.14 (2.00, 2.28); <0.01	0.28 (0.22, 0.37); <0.01	0.47 (0.41, 0.53); <0.01	1.22 (1.10, 1.36); <0.01	3.23 (2.88, 3.63); <0.01	1.99(1.87, 2.12); <0.01
Sex HR/OR (95% CI); p	0.55 (0.48, 0.63); <0.01	0.57 (0.50, 0.65); <0.01	0.57 (0.50, 0.65); <0.01	0.58 (0.51, 0.66); <0.01	0.57 (0.50, 0.65); <0.01	0.59 (0.52, 0.67); <0.01
Cigarettes per day HR/OR (95% CI); p	1.00 (0.99, 1.02); 0.56	1.00 (0.99, 1.01); 0.82	1.00 (0.99, 1.01); 0.83	1.00 (0.99, 1.02); 0.91	1.00 (0.99, 1.02); 0.49	1.00 (0.99, 1.02); 0.60
Sex * cigarettes per day HR/OR (95% CI); p	1.01 (1.00, 1.02); 0.02	1.01 (1.00, 1.02); 0.13	1.01 (1.00, 1.02); 0.11	1.01 (1.00, 1.02); 0.17	1.01 (1.00, 1.02); 0.09	1.01 1.00, 1.02); 0.04

b. Model 2 (Number of Pre-existing Conditions)

	Proportional Hazards (Hazard Rate Ratio)					Poisson (Incidence Rate Ratio)
Model 2	mortality ~ preexisting + age + sex + cigarettes per day + sex * cigarettes per day					
	Without stratification	With stratification				
		pre0: agecat 1 pre1: agecat 1 pre2: agecat 1	agecat 2 agecat 2 agecat 2	agecat 3 agecat 3 agecat 3	agecat4 agecat4 agecat4	
AIC	22991.10	23536.72 23709.81 23625.25	23488.12 23662.85 23601.53	23658.50 23850.00 23775.22	23276.52 23416.57 23357.07	6788.46
Metabolic syndrome HR/OR (95% CI); p	1.06 (0.83, 1.36); 0.62	1.14 (0.89, 1.45); 0.31 0.98 (0.77, 1.25); 0.88 0.89 (0.70, 1.13); 0.35	1.22 (0.95, 1.56); 0.12 1.05 (0.82, 1.34); 0.71 0.94 (0.74, 1.19); 0.60	1.21 (0.95, 1.55); 0.12 1.04 (0.82, 1.33); 0.73 0.92 (0.73, 1.19); 0.57	1.16 (0.91, 1.48); 0.24 1.00 (0.78, 1.27); 0.97 0.91 (0.71, 1.15); 0.33	1.06 (0.82, 1.34); 0.66
Age HR/OR (95% CI); p	2.14 (2.01, 2.28); <0.01	0.27 (0.21, 0.36); <0.01 0.25 (0.19, 0.32); <0.01 0.24 (0.18, 0.31); <0.01	0.45 (0.40, 0.51); <0.01 0.43 (0.38, 0.48); <0.01 0.43 (0.38, 0.49); <0.01	1.24 (1.12, 1.38); <0.01 1.31 (1.18, 1.46); <0.01 1.34 (1.21, 1.49); <0.01	3.42 (3.05, 3.83); <0.01 3.74 (3.34, 4.19); <0.01 3.44 (3.34, 4.19); <0.01	1.99 (1.87, 2.12); <0.01
Sex HR/OR (95% CI); p	0.54 (0.48, 0.62); <0.01	0.58 (0.51, 0.66); <0.01 0.57 (0.52, 0.64); <0.01 0.56 (0.49, 0.64); <0.01	0.58 (0.51 0.66); <0.01 0.59 (0.52, 0.67); <0.01 0.58 (0.51, 0.66); <0.01	0.59 (0.52, 0.67); <0.01 0.59 (0.52, 0.67); <0.01 0.57 (0.50, 0.65); <0.01	0.58 (0.51, 0.66); <0.01 0.59 (0.52, 0.67); <0.01 0.58 (0.51, 0.66); <0.01	0.59 (0.51, 0.67); <0.01
Cigarettes per day HR/OR (95% CI); p	1.00 (0.99, 1.02); 0.72	1.00 (0.99, 1.01); 0.74 1.00 (0.99, 1.01); 0.89 1.00 (0.99, 1.01); 0.95	1.00 (0.99, 1.01); 0.94 1.00 (0.99, 1.02); 0.72 1.00 (0.99, 1.02); 0.50	1.00 (0.98, 1.01); 0.84 1.00 (0.99, 1.01); 0.97 1.00 (0.99, 1.01); 0.79	1.00 (0.99, 1.02); 0.63 1.00 (0.99, 1.02); 0.46 1.01 (0.99, 1.02); 0.26	1.00 (0.99, 1.02); 0.69
Sex * cigarettes per day HR/OR (95% CI); p	1.01 (1.00, 1.02); 0.01	1.01 (1.00, 1.02); 0.19 1.00 (0.99, 1.01); 0.38 1.00 (0.99, 1.01); 0.24	1.01 (1.00, 1.02); 0.15 1.00 (0.99, 1.01); 0.37 1.00 (0.99, 1.01); 0.44	1.00 (1.00, 1.02); 0.26 1.00 (0.99, 1.01); 0.51 1.00 (0.99, 1.01); 0.50	1.01 (1.00, 1.02); 0.09 1.01 (1.00, 1.02); 0.21 1.01 (1.00, 1.02); 0.28	1.01 (1.00, 1.02); 0.03
Preexisting conditions HR/OR (95% CI); p	1.98 (1.82, 2.16); <0.01	0.39 (0.35, 0.44); <0.01 1.86 (1.68, 2.07); <0.01 4.77 (4.01, 5.68); <0.01	0.38 (0.35, 0.43); <0.01 1.91 (1.72, 2.12); <0.01 4.52 (3.80, 5.39); <0.01	0.37 (0.33, 0.41); <0.01 1.98 (1.78, 2.20); <0.01 5.12 (4.30, 6.10); <0.01	0.43 (0.39, 0.48); <0.01 1.71 (1.54, 1.90); <0.01 3.67 (3.07. 4.38); <0.01	1.81 (1.66, 1.97); <0.01

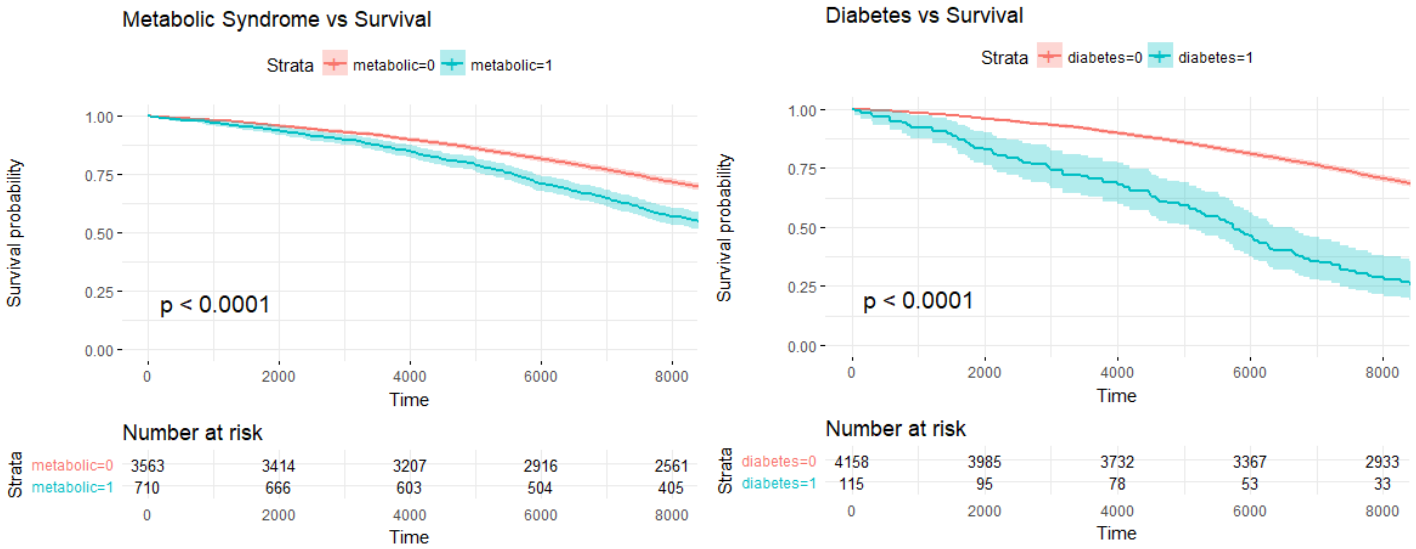

Figure 1. (a) Survival curves for people with metabolic syndrome and people without metabolic syndrome. The orange curve is the survival curve for people who didn't have proxy metabolic syndrome; the green curve is the survival curve for people who had proxy metabolic syndrome. The p-value for the log rank test for these two groups is <0.0001. (b) Survival curves for people with diabetes and people without diabetes. The orange curve is the survival curve for people who didn't have diabetes; the green curve is the survival curve for people who had diabetes. The p-value for the log rank test for these two groups is <0.0001.

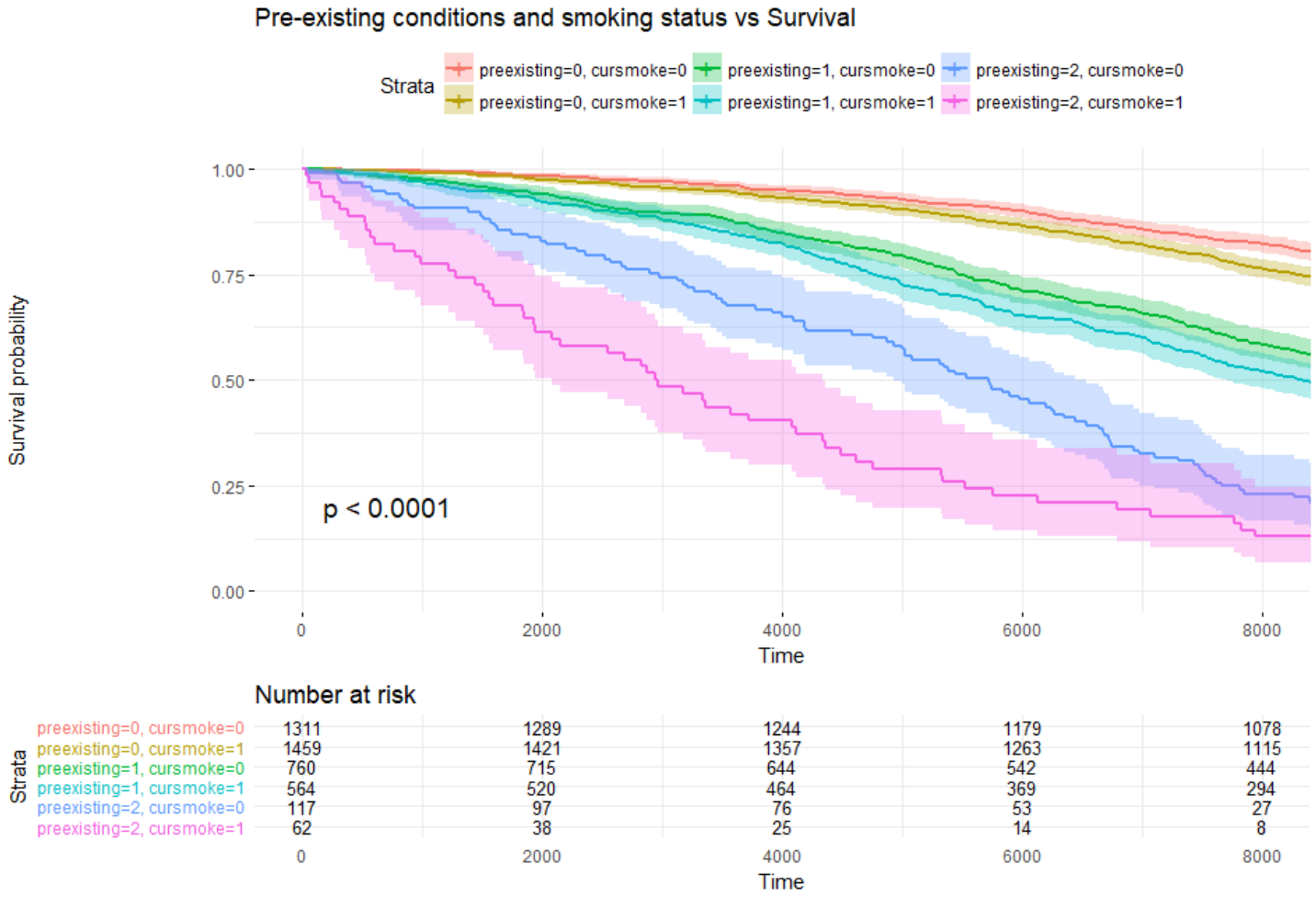

Figure 2. Survival curves for people with different pre-existing conditions. The red curve is the survival curve for people who didn't have pre-existing conditions and were non-smokers; the yellow curve is the survival curve for people who didn't have pre-existing conditions and were current smokers; the green curve is the survival curve for people who had one pre-existing conditions and were non-smokers; the cyan curve is the survival curve for people who had one pre-existing condition and were current smokers; the blue curve is the survival curve for people who had two or more pre-existing conditions and were non-smokers; the pink curve is the survival curve for people who had two or more pre-existing conditions and were current smokers.